Use and safety of anthroposophic medications in chronic disease: A two-year prospective analysis

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Abstract

Background and objective: Anthroposophic medications (AMED) are prescribed by physicians in 56 countries worldwide and are used for the treatment of a variety of conditions. However, safety data on long-term use of AMED from large prospective studies are sparse. The objective of this analysis was to determine the frequency of patient-reported and physician-assessed adverse drug reactions (ADRs) from AMED in outpatients using AMED for chronic diseases over a two-year period.

Methods: We conducted a prospective observational cohort study involving 131 medical practices in Germany. In total, 662 consecutive outpatients aged 1-75 years were enrolled in the study. The patients were using AMED for mental (primarily depression and fatigue), musculoskeletal, respiratory, neurological, and other chronic diseases. Main outcome measures were use of AMED and ADRs to AMED.

Results: Throughout the two-year follow-up, patients used 949 different AMED for a total of 11 487 patient months. The origin of AMED was mineral (8.1%, 77 of 949

AMED), botanical (41.8%), zoological (7.8%), chemically defined (10.5%) and mixed (31.7%). Most frequently used AMED ingredients were *Viscum album* (11.5%, 76 of 662 patients), *Bryophyllum* (9.4%), *Arnica* (7.9%), and Silicea (7.7%). Non-AMED products were used by 94.2% of patients for a total of 11 202 patient-months; 45.2% of this use was accounted for by medication for the CNS, the cardiovascular system and the alimentary tract and metabolism.

A total of 1861 adverse events (AEs) were documented. The most frequent AEs were non-specific symptoms, signs and findings (*International Classification of Diseases* [10th Edition] R00-R99: 27.6%, 513 of 1861 AEs), musculoskeletal (M00-M99: 16.9%), respiratory (J00-J99: 8.2%) and digestive diseases (K00-K93 6.6%). No serious AEs attributable to any medication occurred. Out of the 1861 reported AEs, 284 (15.3%) AEs were suspected by the physician or the patient to be an adverse reaction to non-medication therapy (n = 42 AEs), non-AMED (n = 187), or AMED (n = 55 AEs in 29 patients). Twenty of these 29 patients had confirmed ADR to 21 AMED. These ADRs were local reactions to topical application (n = 6 patients), systemic hypersensitivity (n = 1), and aggravation of pre-existing symptoms (n = 13). In ten patients, AMED was stopped due to ADRs; two patients had ADR of severe intensity. Median number of days with ADRs was 7 (range 1-39) days. All ADRs subsided, none were serious. The frequency of confirmed ADRs to AMED was 2.2% (21 of 949) of all different AMED used, 3.0% (20 of 662) of AMED users and one ADR per 382 patient-months of AMED use.

Conclusion: In this two-year prospective study, AMED was a safe treatment.

Background

Anthroposophic medicine (AM) is a system of medicine founded by Rudolf Steiner and Ita Wegman.[1] AM is provided by physicians in 56 countries worldwide.[2] A cornerstone of AM therapy is AM medication (AMED). AMED includes preparations of mineral, botanical or zoological origin, as well as chemically defined substances.[3] All AMED are manufactured according to good manufacturing practice and national drug regulations; quality standards of raw materials and manufacturing methods are described in the *Anthroposophical Pharmaceutical Codex*.[3]

The manufacturing of AMED often includes pharmaceutical processes that are rarely used for non-AMED products, e. g. the production of metal mirrors by chemical vapour decomposition, and the processing of herbs by fermentation, toasting, carbonising, incineration or digestion (heat treatment at 37°C).[3] Thus, in a given AMED, the concentration of active ingredients may differ markedly from that of corresponding non-AMED products of the same origin. Moreover, AMED can be prepared in concentrated form or in homoeopathic potencies; out of 7855 different AMED in current use (the number accounts for different concentrations of the same AMED as well as different pack sizes) 55% consist exclusively of ingredients in a decimal potency of D6 or higher, i. e. in a dilution ≤ 1/1 000 000 of the original ingredient. AMED can be delivered in various administration routes (i. e. oral, rectal, vaginal, conjunctival, nasal or percutaneous application, or by subcutaneous, intracutaneous or intravenous injection).

In Europe, AMED are prescribed by approximately 30 000 physicians.[4] In Germany, approximately 12 million dose packs of AMED were sold in 2005.[5] Notably, the pattern of use is extremely skewed: whereas the top 20 selling AMED products together amount to more than one-third of the turnover, 88% of all individual AMED are sold in quantities of <1000 packs per year.[5] In summary: with respect to

manufacturing, dose range, administration forms, and pattern of use, AMED differs from homoeopathic, herbal and conventional medications.

Almost all AMED in current use have been on the market since the 1970s, some AMED even since the 1920s. Pre-clinical testing, pharmacovigilance reports, surveys, and 190 clinical studies suggest that adverse drug reactions (ADRs) to AMED are infrequent and mostly mild to moderate in severity.[6] However, safety data from the clinical trials are often sparse, and in two-thirds of the trials, the number of patients using AMED was <100.[6] Possible ADR mechanisms include local reactions to topical AMED application and systemic hypersensitivity. Toxic reactions are also possible, but for substances with known toxic properties, e. g. *Aconite* and *Belladonna*, the daily doses used in AMED therapy are 100-1000 times lower (or less) than the doses known to cause toxicity.

The Anthroposophic Medicine Outcomes Study (AMOS)[7] provided an opportunity to investigate the use and safety of AMED in a large patient sample. AMOS was a prospective, long-term cohort study of patients starting AMED or non-medication AM therapies (art, eurythmy movement, massage) for various chronic diseases. A 2-year analysis showed substantial reduction of disease severity and improvement of quality of life without cost increase.[7;8] At each follow-up, patients and physicians documented adverse events (AE). In the primary analysis of this study [7], AE reported as suspected of being an ADR to AMED or other medication were not further investigated but were all classified as ADRs. Here we present a more detailed analysis of the use and safety of AMED in AMOS patients.

Methods

Objective and design

The objective was to investigate the pattern of AMED use and to determine the frequency of patient-reported and physician-assessed ADRs to AMED in outpatients using AMED for chronic diseases over a 2-year period. For this purpose, we analysed patient self-reports of medication use as well as patient and physician reports of AEs in a prospective cohort study.

Setting, participants, and therapy

The study was initiated by a health insurance company as part of a research program on the effectiveness, safety and costs of AM therapies in chronic disease.[7] All physicians certified by the Physicians' Association for Anthroposophical Medicine in Germany and working in an office-based practice or outpatient clinic were invited to participate in the study. The participating physicians recruited consecutive patients starting AMED or non-medication AM therapy. Patients enrolled in the period 1 Jan 1999 to 31 March 2001 were included in the present analysis (18- and 24-month follow-ups were not performed for patients enrolled before 1 January 1999) if they fulfilled eligibility criteria.

The following inclusion criteria were used: (i) Outpatients aged 1-75 years; (ii) referral to AM therapy (art, eurythmy or rhythmical massage), or initial AM-related consultation ≥30 minutes for any indication (main diagnosis); (iii) use of at least one AMED (any medication produced by Abnoba Arzneimittel GmbH, Pforzheim, Germany; Helixor Heilmittel GmbH & Co, Rosenfeld, Germany; WALA Heilmittel GmbH, Eckwälden, Germany; or Weleda AG, Schwäbisch-Gmünd, Germany) within 2 years after study enrolment.

Patients were excluded if they had previously received the AM therapy in question (see [ii] of inclusion criteria) for their main diagnosis.

Outcomes

Medication use was assessed as the number of patient-months of all medications (AMED and non-AMED) used within the first 2 years after study enrollment. Description of the AMED (origin, ingredients, administration route, administration frequency) and non-AMED products (Anatomical Therapeutic Chemical (ATC) groups, administration frequency) were also recorded.

AE data such as frequency, diagnosis, intensity (mild/moderate/severe = no/some/complete impairment of normal daily activities, respectively), seriousness (a serious AE being an event that leads to acute hospital admission, permanent health damage or death) and whether the AE had a causal relationship to the AMED (probable, possible, improbable, no relationship, unable to evaluate) were assessed. In addition, the most probable cause of the AE (AMED, other medication, primary or concomitant illness, other) was noted.

Events with probable or possible causal relationship to AMED therapy were classified as confirmed ADRs to AMED for the purpose of this analysis: The name, duration, intensity and seriousness of these ADRs was recorded.In addition, we noted the necessary actions taken against the ADRs (none, dose reduction of medication, withdrawal of medication, admit to hospital, therapeutic counteractions, other) and the outcome of the ADR (subsided, permanent health damage, patient died). Other variables assessed in this study include whether the ADR was expected (yes: ADR previously reported or may be expected because of known mechanism of action of ingredients) and the frequency of confirmed ADRs to AMED in relation to the number of patients, the number of different AMED used and the duration of use.

Data collection

All data were documented with questionnaires sent in sealed envelopes to the study office. At study enrollment, physicians documented primary and concomitant diseases; patients (for children: legal guardians) documented socio-demographic data and symptom severity. Physicians documented all prescribed medication at each visit during the first 12 months of the study (name, administration route and change in dosage or withdrawal of medication). Patients documented medication use in the preceding 3 (or 6) months at each follow-up after 3, 6, 12, 18 and 24 months (name, administration frequency [daily, 3-6 days per week, 1-2 days per week, 1-3 days per month, < 1 day per month] and duration of use). AEs were defined as any new health complaint requiring medical attention (regardless of causal relationship with medication or therapies) and were documented by patients after 3, 6, 12, 18 and 24 months (name, intensity). AEs suspected to be adverse reactions from medication or therapies were documented by patients after 6, 12, 18 and 24 months and by physicians after 3, 6, 9 and 12 months (date, name of AE, intensity, suspected cause, therapy withdrawal due to AE). Any missing data in the documentation of suspected adverse reactions were completed by telephone monitoring (for physicians' documentation also by on-site monitoring). Physicians were compensated €40 per included and fully documented patient; patients received no compensation.

Data were entered twice by two different persons into Microsoft® Access 97. The two datasets were compared and discrepancies resolved by checking with the original data.

For patients with AEs suspected to be ADRs to AMED, physicians and patients were contacted by telephone and the following items were checked: concomitant illness and ongoing therapy at time of the AE, necessary actions against AE, duration and outcome of AE and expectedness of AE. In case of discordant physician/patient documentation

of AE intensity, the highest intensity was used. If documentation of AE duration entailed a possible range, the highest number of days was used. Information about expected ADRs to these AMED was obtained from the manufacturers.

AEs were coded according to the Tenth Edition of the *International Classification of Diseases* (ICD-10); confirmed ADR were also coded according to Medical Dictionary for Regulatory Activities (MedDRA).

Quality assurance, adherence to regulations

The study was approved by the Ethics Committee of the Faculty of Medicine Charité, Humboldt University, Berlin, Germany, and was conducted according to the Helsinki Declaration and the International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all patients before enrollment.

Data analysis

Statistical analysis (SPSS® 13.0.1, StatXact® 5.0.3) was descriptive. For analysis of medication use, missing data on administration frequency were replaced by the value 3/7 (three times weekly) for AMED ampoules for injection, and 1 (daily) for all other medications; missing data on duration of AMED or non-AMEd use were replaced by average duration of AMED and non-AMED use, respectively, during the follow-up period in question. AMED with identical ingredients and dosage form but different concentrations were grouped together. For each medication, the number of patient-months was calculated as ‘duration of use’ x F (where F = 1 for medication taken daily, 3-6 days per week or 1-2 days per week; F = 1/15 for medication taken 1-3 days per month; F = 0 for medication taken < 1 day per month). The number of patient-months for all AMED, all non-AMEDs and for relevant medication subgroups was calculated as the sum of all patient-months in question.

All AEs were subject to descriptive analysis. Based on existing data on adverse effects of herbal remedies[9;10], a list of 'target AE' diagnoses was defined to identify possible cases of toxicity (heart, liver, kidney, pancreas, nervous system) or congenital malformations (ICD-10: G40-G41, G61-G63, I40-I42, I46, I50, K71-K74, K85, N00-N05, N17-N19, Q00-Q99, R56-R57).

All Target AEs, serious AEs, and AEs reported as suspected to be ADRs to AMED were analysed individually. The causal relationship of these AEs to the use of AMED was classified by the first author according to pre-defined criteria: probable, possible, improbable, no relationship, unable to evaluate (table I).

Table I Criteria for classification of causal relationship between adverse events and medication[11]

Probable

- Rational temporal relationship to the time of intake of the medication.
- AE is already known to be a side effect of the medication or may be expected.
- Regression or disappearance of the AE after discontinuation of medication or dose reduction.
- Reappearance of the AE after repeated exposure.
- AE cannot be explained in a reasonable manner by the clinical state of the patient.

Possible

- Rational temporal relationship to the time of intake of the medication.
- AE is already known as a side effect of the medication or may be expected.
- AE could be explained by numerous other factors.

Improbable

- Rational temporal relationship to the time of intake of the medication.
- AE has not been reported so far as a side effect of the medication or cannot be expected.
- AE persists after discontinuation of the medication or dose reduction.
- Repeated exposure does not lead to reappearance of the AE.
- AE could be explained by numerous other factors.

No relationship

- No rational temporal relationship to the time of intake of the medication.
- AE is evidently caused by other factors, e.g. symptom of a concomitant disease.

Unable to evaluate

- Amount and content of data do not permit a judgment of the relationship to the medication.

Results

Participating physicians

A total of 131 physicians enrolled patients into the study; these physicians did not differ significantly from all AM-certified physicians in Germany (n = 362) regarding sex (56.5 vs. 62.2% males, respectively, p = 0.297), age (mean ± SD 46.3 ± 7.2 vs. 47.5 ± 7.9 years, p = 0.213), number of years in practice (17.8 ± 7.6 vs. 18.9 ± 7.3 years, p = 0.371), or the proportion of primary care physicians (87.8 vs. 85.0%, p = 0.470).

Patient recruitment and follow-up

From 1 January 1999 to 31 March 2001, a total of 999 patients were assessed for eligibility. Of these patients, 662 fulfilled all eligibility criteria and were included in the analysis. Of the 337 patients who were not included, 188 patients were not included in the AMOS study (reasons: patients' baseline questionnaire missing [n = 57], physician's baseline questionnaire missing [n = 26], patients' and physician's baseline questionnaire dated > 30 days apart [n = 58], no informed consent [n = 7], other reasons [n = 40]). The remaining 149 patients were participants in the AMOS study but were not included in this analysis (reasons: no follow-up data [n = 17], no documented AMED use [n = 132]). Included and not included patients did not differ significantly regarding age, sex, diagnosis, disease duration, baseline disease severity or baseline symptom severity. The last patient follow-up ensued on 30 April 2003.

A total of 70.8% (469 of 662) of patients were enrolled by general practitioners, 15.1% by paediatricians, 5.7% by internists and 8.3% by other specialists. The physicians' settings were primary care practices (87.9% of patients, n = 582 of 662), referral practices (5.3%) and outpatient clinics (6.8%). Each physician enrolled a median of 3.0 patients (interquartile range [IQR] 2.0-7.0 patients).

The 662 evaluable patients and the 17 patients excluded from analysis because of no follow-up data were each administered five follow-up questionnaires (3395 questionnaires in total), of which 2984 (87.9%) questionnaires were returned. Follow-up rates of evaluable patients were 97.3% (644 of 662), 94.3%, 91.2%, 85.6%, and 82.3% after 3, 6, 12, 18 and 24 months, respectively. Documentation of AMED use was complete for 91.2% of AMED use records and incomplete (frequency and/or duration of use lacking) for 8.8%.

Baseline characteristics

Disease status

Most frequent diagnoses, classified by ICD-10, were F00-F99 Mental Disorders (29.8%, 197 of 662 patients), M00-M99 Musculoskeletal Diseases (19.8%), J00-J99 Respiratory Diseases (9.7%), and G00-G99 Nervous System Diseases (7.3%). Most common diagnosis groups were Spinal Diseases (ICD-10 M40-M54: 13.6%, 90 of 662), Mood Disorders (F31-F39: 9.2%), Asthma/Sinusitis/Bronchitis (J32, J40-J42, J44-J45: 6.6%), Fatigue (F48: 5.4%) and Headache (G43-G44, R51: 4.7%). The median disease duration was 3.0 (IQR 0.8-8.5) years. Patients had a median of 2.0 (IQR 1.0-3.0) comorbid diseases. The most common comorbid diseases, classified by ICD-10, were M00-M99 Musculoskeletal Diseases (15.2%, 171 of 1124 diagnoses) and F00-F99 Mental Disorders (14.1%).

Socio-demographic *data*

Patients were recruited from 15 of 16 German federal states. Age groups were 0-19 years (24.6%, 163 of 662 patients), 20-39 years (27.9%), 40-59 years (37.5%) and 60-75 years (10.0%) with a median age of 39.0 (IQR 22.8-48.0) years. 72.7% (481 of 662 patients) were women. Compared with the German population, the socio-demographic profile of the study participants was more favourable for education, occupation, alcohol, smoking and being overweight; similar for unemployment, low-income, living alone,

severe disability status and sport; and less favourable for work disability pension and sick-leave (table II).

Table II Socio-demographic data

Characteristics	Adult study patients [n (%)]	Adult German population (%)	Reference
”Fachhochschule” or university entrance qualification	289/505 (57)	19	[12]
University degree	133/503 (26)	6	[12]
Wage earners	16/505 (3)	18	[12]
Unemployed during last 12 months[a]	22/263 (8)	10	[12]
Living alone	106/499 (21)	21	[12]
Net family income < 900 € per month	62/428 (14)	16	[12]
Alcohol use daily (patients) vs. almost daily (Germany)			
male	4/97 (4)	28	[13]
female	10/408 (2)	11	
Regular smoking			
male	22/97 (23)	37	[14]
female	65/406 (16)	28	
Sports activity ≥ 1 hour weekly (age 25-69 years)	211/465 (45)	39	[15]
Body mass index ≥ 25 (overweight)			
male	22/96 (23)	56	[12]
female	98/402 (24)	39	
Permanent work disability pension	42/505 88)	3	[16]
Severe disability status	48/505 810)	12	[17]
Sick leave days in the last 12 months (mean ± SD) [a]	32.5 ± 66.9	17.0	[18]
[a]Analysed in economically active patients			

Medication use

Throughout the 24-month follow-up, patients used 949 different AMED products for a total of 11 487 patient-months. Of the AMED products, 648 had a single ingredient of mineral, botanical, zoological or chemically defined origin, with a total of 265 different ingredients (table III). The 20 most frequently used AMED ingredients are listed in table IV; the 20 most common individual AMED are listed in table V. The most common administration forms were dilutions for oral use (30.9%, 293 of 949 AMED), ampoules for injection (21.7%), globuli (17.6%), powders (10.1%) and ointments (7.3%). Administration frequency for AMED was daily (70.2%, 3600 of 5130 documentations), 3-6 days per week (9.7%), 1-2 days per week (10.9%), 1-3 days per month (4.2%), <1 day per month (1.2%), unknown (3.8%).

Table III Origin of anthroposophic medications

Origin of medication	Different ingredients [n]	Different medications [n (%)]	Patients using medication [n (%)][a]	Patient-months [n (%)]
Mineral	44	77 (8.1)	203 (30.7)	846 (7.4)
Botanical	124	397 (41.8)	535 (80.8)	5076 (44.2)
Zoological	51	74 (7.8)	141 (21.3)	616 (5.4)
Chemically defined	46	100 (10.5)	305 (46.1)	1 305 (10.9)
Mixed**		301 (31.7)	477 (72.1)	3 499 (30.5)
Not documented			65 (9.8)	145 (1.3)
Total		949 (100.0)	662 (100.0)	11 487 (100.0)

[a] Multiple responses possible
[b] Mixed: Combinations of mineral, botanical, zoological or chemically defined

Table IV Most frequently used ingredients of anthroposophic medications (excluding medication with more than one ingredient)

Ingredient	Origin	Different medications [n (%)]	Patients using nedication [n (%)][a]	Patient-months [n (%)]
Viscum album	Botanical	25 (2.6)	76 (11.5)	660 (5.7)
Bryophyllum (Kalanchoe pinnata)	Botanical	9 (0.9)	62 (9.4)	254 (2.2)
Gentiana lutea	Botanical	8 (0.8)	42 (6.3)	187 (1.6)
Quartz (Silicea)	Chemically defined	7 (0.7)	51 (7.7)	182 (1.6)
Phosphorus	Chemically defined	4 (0.4)	42 (6.3)	167 (1.5)
Cuprum metallicum	Chemically defined	9 (0.9)	41 (6.2)	149 (1.3)
Colchicum autumnale	Botanical	5 (0.5)	17 (2.6)	125 (1.1)
Arnica montana	Botanical	11 (1.2)	52 (7.9)	124 (1.1)
Chelidonium majus	Botanical	7 (0.7)	25 (3.8)	122 (1.1)
Atropa belladonna	Botanical	9 (0.9)	34 (5.1)	115 (1.0)
Aurum metallicum	Chemically defined	4 (0.4)	28 (4.2)	106 (0.9)
Argentum metallicum	Chemically defined	5 (0.5)	25 (3.8)	97 (0.8)
Stibium metallicum	Chemically defined	4 (0.4)	27 (4.1)	91 (0.8)
Conchae (Calcarea carbonicum ostrearum)	Zoological	4 (0.4)	21 (3.2)	88 (0.8)
Equisetum arvense	Botanical	10 (1.1)	24 (3.6)	82 (0.7)
Formica rufa	Zoological	2 (0.2)	18 (2.7)	82 (0.7)
Cichorium intybus	Botanical	8 (0.8)	17 (2.6)	80 (0.7)
Ferrum sidereum (Meteoric iron)	Mineral	5 (0.5)	29 (4.4)	76 (0.7)
Hypericum perforatum	Botanical	8 (0.8)	27 (4.1)	73 (0.6)
Scorodite	Mineral	4 (0.4)	17 (2.6)	67 (0.6)
All other medications		801 (84.4)		8560 (74.5)
Total		949 (100.0)	662 (100.0)	11487 (100.0)

[a] Multiple responses possible

Table V Most frequently used individual anthroposophic medications

Medication	Administration form[a]	Ingredients	Manu-facturer	Patients using medication [n (%)][a]	Patient-months [n (%)]
Hepatodoron®	Tablets	1 tablet contains: *Fragaria vesca*, Folium sicc. 40 mg / *Vitis vinifera*, Folium sicc. 40 mg.	Weleda	70 (10.6)	429 (3.7)
Cardiodoron®	Liquid	10 g (= 10.3 ml) contains: Ethanol. Digestio (1:3.1) from *Onopordum acanthium*, Flos rec. with 1% *Hyoscyamus niger*, Herba rec. Ø 1.0 g / ethanol. Digestio (1:3.1) from *Primula veris*, Flos rec., with 1% *Hyoscyamus niger*, Herba rec. Ø 1.0 g.	Weleda	51 (7.7)	270 (2.4)
Abnobaviscum	Ampoules	*Viscum album* (subspecies abietis / aceris / amygdali / betulae / crataegi / fraxini / mali / pini / quercus) ex herba, pressed juice 20 / 2 / 0.2 / 0.02 mg/ml / D6 / D10 / D20 / D30	Abnoba	30 (4.5)	250 (2.2)
Iscador	Ampoules	*Viscum album* (subspecies mali / pini / quercus / ulmus) ex herba, fermented aqueous extract 20 / 10 / 1 / 0.1 / 0.01 / 0.001/ 0.0001 mg/ml	Weleda	22 (3.3)	171 (1.5)
Bryophyllum 50%	Powder	*Bryophyllum*, Folium 50%	Weleda	22 (3.3)	132 (1.1)
Phosphorus	Liquid	Phosphorus D6 / D8 / D10 / D12 / D20 / D25 / D30	Weleda	33 (5.0)	126 (1.1)
Disci comp. cum Stanno	Globuli	10 g contains Disci intervertebrales bovis (cervicales, thoracici et lumbales) D5 0.1 g, *Equisetum arvense* ex herba ferm D14 0.1 g, *Formica rufa* ex animale toto D6 0.1 g, *Phyllostachys* e nodo ferm D5 0.1 g, Stannum metallicum D5 0.1 g	Wala	15 (2.3)	108 (0.9)
Vitis comp.	Tablets	1 tablet contains: Calcarea formicica D2 20 mg, Fragaria vesca, Folium sicc. 40mg, Stibium metallicum praeparatum D5 20mg, Vitis vinifera, Folium sicc. 40mg.	Weleda	11 (1.7)	107 (0.9)
Digestodoron®	Liquid	10 g (= 9.4 ml) contains: 1.8 g ethanol. Digestio (1:3.1) from *Dryopteris filixmas*, Folium rec., 0.4 g ethanol. Digestio (1:3.1) from *Polypodium vulgare*, Folium rec., 4 g ethanol. Digestio (1:3.1) from *Salix alba*, purpurea, viminalis, Folium rec. 1.8 g ethanol. Digestio (1:3.1) from *Phyllitis scolopendrium*, Folium rec.	Weleda	17 (2.6)	92 (0.8)
Aurum / Hyoscyamus comp.	Liquid	10 g (= 10.2 ml) contains: Aurum metallicum praeparatum Dil. D10 3.34 g, Hyoscyamus D5 3.34 g, Stibium metallicum praeparatum D6 3.34 g.	Weleda	14 (2.1)	86 (0.7)
Silicea (Quartz)	Liquid	Silicea D8 / D10 / D12 / D20 / D30 / D60	Weleda	24 (3.6)	79 (0.7)
Calciodoron AM	Powder	10 g contains: Apatite D5 1 g, *Cucurbita pepo*, Flos rec. D2 1 g	Weleda	12 (1.8)	77 (0.7)
Helixor	Ampoules	*Viscum album* (subspecies abietis / mali / pini) ex herba recente, aqueous extract 1:20: 0.01 / 0.1 / 1 / 5 / 10 / 20 / 30 / 50 / 100 mg.	Helixor	8 (1.2)	76 (0.7)
Colchicum, Tuber ethanol. Digestio	Liquid	*Colchicum*, Tuber D1 / D2 / D3 / D4 / D5 / D6 / D10 / D12 / D30	Weleda	11 (1.7)	75 (0.7)
Scleron®	Tablets	1 tablet contains: Plumbum mellitum (prepared from lead, honey and cane sugar) D12 250 mg	Weleda	12 (1.8)	74 (0.6)

Gentiana Stomach Pellets	Globuli	10 g contains *Artemisia absinthium* ex herba, Infusum Ø (=D1) 0.45 g, *Gentiana lutea* e radice, Decoctum Ø (=D1) 0.45 g, *Strychnos nux-vomica* e semine ferm D4 0.10 g, *Taraxacum officinale* e planta tota ferm Ø 0.05 g	Wala	15 (2.3)	73 (0.6)
Cartilago/Mandragora comp.	Globuli	10 g contains Antimonit D5 0.1 g, Argentum metallicum D7 0.1 g, *Betula* e foliis ferm. D4 0.1 g, Cartilago articularis bovis D7 0.1 g, *Mandragora officinaru*m e radice ferm D4 0.1 g	Wala	11 (1.7)	72 (0.6)
Ferrum ustum comp.	Powder	10 g contains: *Anisi* fructus 2.5 g, Ferrum ustum D3 2.5 g, Nontronit D3 2.5 g, *Urtica dioica*, Herba D4 2.5 g.	Weleda	15 (2.3)	70 (0.6)
Bryophyllum Liquid	Liquid	*Bryophyllum* Ø / D1 / D3 / D4 / D6	Weleda	24 (3.6)	68 (0.6)
Gentiana lutea, ethanol. Decoctum	Liquid	*Gentiana lutea* Ø / D1 / D2 / D4 / D4	Weleda	18 (2.7)	67 (0.6)
Other medications				640 (96.7)	8983 (78.2)
Total				662 (100.0)	11487 (100.0)

[a] Administration form: Ampoules = Liquid dilution / solution for injection. Liquid = Dilution / mother tincture for oral use.

[b] Multiple responses possible.

/: Medication exists in different concentrations grouped together. Ø: mother tincture. D: Decimal potencies (1:10 dilution; e.g. D3 = 1:1000)

Non-AMED products were used by 94.2% (603 of 662) of patients. In total 11 202 patient-months of non-AMED use were documented, 45.2% of this use was accounted for by medication for the CNS, the cardiovascular system and the alimentary tract and metabolism (ATC-groups N, C, and A, table VI). Administration frequency for non-AMED did not differ significantly from that of AMED ($p = 0.723$).

Overlap of AMED and non-AMED of identical origin was investigated among the 20 most commonly used AMED ingredients. One overlapping non-AMED herb was found (*Thuja*), used by one patient.

Table VI Use of non-anthroposophic medication

Anatomical chemical therapeutic index	Different medications [n (%)]	Patients using nedication [n (%)][a]	Patient-months [n (%)]
A: Alimentary tract and metabolism	227 (14.3)	235 (35.5)	1 662 (14.8)
B: Blood and blood forming organs	37 (2.3)	51 (7.7)	237 (2.1)
C: Cardiovascular system	192 (12.1)	121 (18.3)	1 601 (14.3)
D: Dermatologicals	100 (6.3)	75 (11.3)	355 (3.2)
G: Genito-urinary system and sex hormones	121 (7.6)	136 (20.5)	758 (6.8)
H: Systemic hormonal preparations, excluding sex hormones and insulins	53 (3.3)	74 (11.2)	959 (8.6)
J: Anti-infectives for systemic use	87 (5.5)	112 (16.9)	112 (1.0)
L: Antineoplastic and immunomodulating agents	26 (1.6)	21 (3.2)	230 (2.1)
M: Musculo-skeletal system	132 (8.3)	137 (20.7)	493 (4.4)
N: Nervous system	236 (14.8)	246 (37.2)	1 801 (16.1)
P: Antiparasitic products, insecticides and repellents	5 (0.3)	5 (0.8)	8 (0.1)
R: Respiratory system	230 (14.5)	237 (35.8)	967 (8.6)
S: Sensory organs	41 (2.6)	35 (5.3)	137 (1.2)
Homoeopathic medication		264 (39.9)	802 (7.2)
Other and not classified		244 (36.9)	1075 (9.6)
Total	1 590 (100.0)	662 (100.0)	11 202 (100.0)

[a] Multiple responses possible

Safety

AEs (new health complaints regardless of causal relationship to medication/therapy) were documented in 503 patients. A total of 1861 AE were documented, with 490 different ICD-10 four-digit diagnoses. The most frequent AEs were R00-R99 Symptoms, Signs and Abnormal Clinical and Laboratory Findings, Not Elsewhere Classified (27.6%, 513 of 1861 AEs), M00-M99 Musculoskeletal Diseases (16.9%), J00-J99 Respiratory Diseases (8.2%) and K00-K93 Digestive Diseases (6.6%). The

most frequent single diagnoses are listed in table VII. Intensity of AEs was mild (21.6%; 397 of 1835 evaluable AEs), moderate (56.9%) and severe (21.4%).

Table VII Adverse events: most frequent ICD-10 four digit diagnoses

ICD-10	Diagnosis	Adverse events [n (%)]	Patients with adverse events [n (%)]
M54.9	Dorsalgia, unspecified	52 (2.8)	43 (6.5)
R51	Headache	58 (3.1)	42 (6.3)
M25.5	Pain in joint	48 (2.6)	40 (6.0)
R53	Malaise and fatigue	47 (2.5)	33 (5.0)
M54.1	Radiculopathy	29 (1.6)	27 (4.1)
J30.1	Allergic rhinitis due to pollen	26 (1.4)	23 (3.5)
F32.9	Depressive episode, unspecified	39 (2.1)	22 (3.3)
R52.9	Pain, unspecific	22 (1.2)	19 (2.9)
K52.9	Noninfective gastroenteritis and colitis, unspecified	18 (1.0)	18 (2.7)
G47.9	Sleep disorder, unspecified	18 (1.0)	17 (2.6)
H93.1	Tinnitus	19 (1.0)	16 (2.4)
R42	Dizziness and giddiness	17 (0.9)	16 (2.4)
M54.2	Cervicalgia	16 (0.9)	16 (2.4)
F41.9	Anxiety disorder, unspecified	18 (1.0)	15 (2.3)
R11	Nausea and vomiting	16 (0.9)	15 (2.3)
	Other diagnoses	1418 (76.2)	
	Total	1861 (100.0)	662 (100.0)

Serious AEs were documented in 15 patients. Eight patients died and in all of them the cause of death was a malignant disease (eight different malignancies) that had been present at study enrollment. Seven patients were acutely hospitalised. One child with posthaemorrhagic hydrocephalus was hospitalised three times for pyelonephritis, febrile convulsions and suspected shunt obstruction, respectively; six patients were hospitalised once each for somatisation disorder with acute anxiety and tachycardia, severe depression, thrombosis of lower extremity, Henoch-Schönlein purpura, suspected pneumonia and intestinal perforation from swallowing fish bones. The median duration of these hospitalisations was 5.5 (range 1-29) days. The patient with thrombosis had sequelae; all other patients recovered completely. None of these AEs were causally related to any medication or therapy.

A Target AE (see Data Analysis for definition) occurred in two patients – R56.0 febrile convulsions (this AE required acute hospitalisation) and R57.9 failure of

peripheral circulation, not otherwise specified (not serious, reported as suspect of adverse reaction to AM eurythmy exercises). Neither of these patients had used any AMED during the last 6 months prior to their AE.

Out of the 1861 reported AEs, 284 (15.3%) AEs were suspected by the physician or the patient to be an adverse reaction to non-medication therapy (n = 42 AEs), non-AMED (n = 187) or AMED (n = 55). The extent of overlap between AE reports concerning non-AMED and AMED with identical ingredients was investigated. Out of 187 AEs associated with non-AMED, 177 AEs were associated with conventional drugs and ten AEs were associated with ten different herbal or homoeopathic medications, two of which overlapped with AMED ingredients: (i) non-AM arsenicum album D6: unspecified psychic disturbances; AMED arsenicum album D10: tinnitus increased; (ii) non-AM chamomile ointment: contact dermatitis; AMED Chamomilla/Malachit comp. dilution: burning eyes.

The 55 AEs suspected to be ADRs to AMED occurred in altogether 29 patients who were using 37 AMED (35 different AMED). The highest intensity of AE was mild (n = 5 patients), moderate (n = 18) and severe (n = 6). No AE was serious. For the 37 AMED in question, the causal relationship to AEs was classified as probable (n = 11 of 37 AMED), possible (n = 10), improbable (n = 10), no relationship (n = 4) and unable to evaluate (n = 2, unclear if any AMED had been used, causal relationship otherwise improbable). In the 29 patients, the most probable cause of their AE was an AMED (n = 20 patients), other medication (n = 1), primary or concomitant illness (n = 7), other (n = 1: transient symptom aggravation due to temporary withdrawal of other medication).

In total, 20 patients (aged 6-72 years, male/female = 8/12) had 30 confirmed ADRs (AEs with possible or probable causal relationship)*:* to 21 AMED (19 different AMED) [table VIII]. These ADRs were documented by physicians (13 AMED, 13 patients), by

Table VIII Confirmed adverse drug reactions from anthroposophic medication (causal relationship probable or possible)[a]

Patient no	Sex	Age (y)	Medication (manufacturer)	Indication	Comorbidity	ADR (MedDRA)	De-challenge	Re-challenge	Causal relation	Expected?	Intensity	Duration (days)	Action[b]
1	f	42	Abnobaviscum® mali 5 and 6 Ampoules s.c. (Abnoba)	Cervical dysplasia, chronic fatigue, depression	Paroxysmal tachycardia, recurrent anaemia, under-weight	General condition reduced	Yes	Yes	Probable	Yes	Sev.	14	Red
						Hypothermia	Yes	Yes	Probable	Yes	Sev.	14	Red
						Dizziness	Yes	Yes	Probable	Yes	Sev.	14	Red
1						Feelings of weakness	Yes	Yes	Probable	Yes	Mod.	5	Red
1											Mild	16	Red
1						Obsessive thoughts	Yes	No	Probable	No	Mod.	1	Red
1						Hyperventilation	Yes	Yes	Probable	No	Mod.	4	Red
1						All ADRs in Patient 1			Probable			39	Red
2	m	58	Iscador® Quercus Series III Ampoules s.c. (Weleda)	Melanoma	Osteoarthritis knee	Injection site reaction	Yes	Yes	Probable	Yes	Mod.	13	Stop
3	f	55	Rosmarin Ointment 10% (Weleda)	Cold feet, migraine	Psoriasis, Spon-dylarthritis psoriatica	Blisters	Yes	No	Probable	Yes	Mod.	3	Stop
4	f	40	Gencydo® 1% Ampoules s.c. (Weleda)	Asthma	Respiratory in-fection	Injection site reaction	Yes	Yes	Probable	Yes	Mod.	14	Stop
5	f	57	Iscador® Mali 10 mg Ampoules s.c. (Weleda)	Breast cancer		Injection site reaction	Yes	Yes	Probable	Yes	Mod.	18	Red
6	f	48	Abnobaviscum® mali 5 and 6 Ampoules s.c. (Abnoba)	Breast cancer		Fatigue	Yes	Yes	Probable	Yes	Mod.	10	No
7	f	47	Oxalis 30% Ointment (Weleda)	Gastro-oesophageal reflux, abdominal cramps	Shoulder-arm syndrome	Allergic exanthema	Yes	Yes	Probable	Yes	Mod.	2	Stop
8	m	7	Phosphorus D12 Liquid (Weleda)	Sleep disturbance		Nervousness	Yes	No	Probable	Yes	Mild	7	Red
9	m	8	Pneumodoron® 2 Liquid (Weleda)	Bronchopneumonia	Hyperactivity, concentration difficulties, phosphate intolerance, dust mite allergy	Hyperactivity syndrome increased	Yes	No	Probable	Yes	Sev.	2	Stop
10	m	8	Gencydo® 0.1% Eyedrops (Weleda)	Allergic rhinoconjuncti-vitis		Burning	Yes	Yes	Probable	Yes	Mild	19	No
11	f	72	Articulatio coxae Gl D6 Ampoules s.c. (Wala)	Hip osteoarthritis	Cardiac arrhythmia	Nausea	Yes	Yes	Probable	Yes	Mod.	4	Stop
						Tinnitus	Yes	Yes					

						Tachycardia	Yes	Yes				
						Sweating	Yes	Yes				
12	m	43	Arsenicum album D10 Liquid (Weleda)	Attention deficit disorder	Tinnitus	Worsening of tinnitus	Yes	No	Possible	No	Mild	21	Stop
13	m	70	Chelidonium Capsules (Weleda)	Headache	Hypertension, liver cirrhosis, annular erythema	Flatulence	Yes	Yes	Possible	Yes	Mod.	3	Red
						Nausea	Yes	Yes					
13			Choleodoron® Liquid (Weleda)						Possible	Yes	Mod.	3	Stop
14	f	57	Gentiana lutea e radice 5% Globuli (Wala)	Scleroderma		Diarrhoea	Yes	No	Possible	No	Mild	21	Red
15	F	39	Stibium metallicum praeparatum D6 10 ml Ampoule i.v. (Weleda)	Grave's disease	Hepatopathy with upper abdominal pain	Palpitations	Yes	No	Possible	No	Mod.	1	Stop
16	m	49	Chelidonium comp. Liquid (Weleda)	Somatoform disorder	Labile hypertension	Aggression	Yes	No	Possible	No	Mod.	7	Stop
17	f	43	Conchae D6 Powder (Weleda)	Generalised anxiety disorder		Dream anxiety disorder	No	No	Possible	Yes	Mod.	5	Stop
18	m	46	Choledoron® Liquid (Weleda)	Depressive disorder	Biliary dysfunction, hypercholesterolaemia	Nausea	Yes	No	Possible	Yes	Mod.	4	Other[c]
19	f	31	Chelidonium Ferro cultum Rh D3 Liquid (Weleda)	Depressive disorder	Chronic borreliosis, obesity, spondylolisthesis, hay fewer	Restlessness	No	No	Possible	No	Mod.	14	Stop
						Logorrhoea	No	No					
20	f	6	Bryophyllum Argento Culto Rh D3 Liquid (Weleda)	Mixed disorder of conduct and emotions		Adjustment disorder with mixed disturbance of emotion and conduct [aggravation]	Yes	Yes	Possible	Yes	Mod.	3	Red

a *Causal relationship and expectedness of ADR were classified by the authors; other items were documented by physicians and patients.

b Actions against ADR (no = no action, red = dose reduction of medication, stop = withdrawal of medication)

c Medication caused ADR due to high alcohol content (64%), was continued with unchanged dosage but diluted in water, and was then tolerated well.

Appl: Number of applications with ADR;.**comp.** = composition; **D** = decimal potencies (1 : 10 dilution; e. g. D3 = 1 : 1^000): **f** = female; **Gl** = mother tincture prepared using glycerol[3] **IV** = intravenous; **m=** male; **MedDRA** = Medical Dictionary for Regulatory Activities; **Mod** = moderate; **Rh** = mother tincture prepared by rhythmic procedure l[3]; **s.c.** = subcutaneous: **Sev.** = severe.

patients (seven AMED, six patients) or by physicians and patients (one AMED). The ADRs were unexpected in 6 of 20 patients. The highest intensity of ADR was mild (n = 4 patients), moderate (n = 14), and severe (n = 2, table IX). ADRs necessitated no change in any AMED (n = 2 patients), dose reduction of AMED (n = 6), withdrawal of some or all AMED (n = 11), or other action (n = 1). Median number of days with confirmed ADR was 7 (range 1-39). ADRs subsided in all patients. No ADR was serious.

Table IX Adverse reactions of severe intensity from anthroposophic medication.

Patient No. 1: A 42-year-old woman with cervical dysplasia (later conized), chronic fatigue, depression, paroxysmal tachycardia, recurrent anaemia, underweight and a history of anaphylactic reactions was treated with subcutaneous injections of Abnobavisum® mali 5 and 6 (Abnoba) twice weekly. On the day of her first injection she felt moderately weak; subsequently she experienced severe hypothermia, dizziness, and aggravation of her general condition for 2 weeks. Medication was temporarily withdrawn for 5 days, whereupon these reactions subsided. After re-challenge, she had various reactions on the day of injection: mild to moderate feeling of weakness, moderate hyperventilation, and transient imperative thoughts. Medication dosage was reduced to Abnobaviscum® mali 30, which was well tolerated. During the treatment period of 5½ months (173 days) she had ADRs for altogether 39 days. (This description is based on physician's prospective documentation. ADRs were also documented by the patient, who rated overall ADR intensity as mild.)
Patient No. 9: An 8-year old boy with allergies, hyperactivity, concentration difficulties and phosphate intolerance was treated for bronchopneumonia with Pneumodoron® 1 liquid (Weleda) alternating with Pneumodoron® 2 liquid (Weleda, contains Phosphorus D4), each four times daily. Immediately after starting Pneumodoron® 2, his hyperactivity deteriorated and became severe. After 2 days, Pneumodoron® 2 was withdrawn (Pneumodoron® 1 was continued); shortly thereafter the hyperactivity subsided.

Throughout the 2-year follow-up, patients used 949 different AMED, of which 21 (2.2%) AMED were associated with confirmed ADR. A total of 662 patients used AMED; in 20 (3.0%) patients, ADRs to AMED occurred. Overall, 11 487 patient-months of AMED use were documented; 30 ADRs (one ADR per 382 patient-months) occurred.

The frequency of confirmed ADR of severe intensity was 0.2% (2 of 949) of AMED, 0.3% (2 of 662) of AMED users and one severe intensity ADR per 2 872 patient-months.

Discussion

This is one of the first detailed analyses[19] of use and safety of AMED within a large prospective cohort study. In outpatients treated by AM physicians and therapists for

chronic disease we found a low frequency of confirmed ADRs to AMED (one ADR in 33 AMED users and one ADR in 382 patient-months with AMED use).

This study's strengths include broad eligibility criteria (encompassing all age groups and all diagnoses), allowing for the inclusion of multimorbid and drug-sensitive patients. Prospective data collection over a 2-year period enabled the detection of ADRs, which are noticed only after repeated drug administration. AEs were documented at each follow-up by patients as well as physicians (instead of relying on spontaneous reporting from physicians only). All serious AEs and all AEs suspected to be ADRs to AMED were subject to thorough analysis of causal relationship to all ongoing medication according to predefined criteria, checking each case with physicians and patients. Follow-up rates were high (overall 88% in 2 years). Moreover, one-third of all AM-certified physicians in Germany participated in the study; participating physicians resembled all eligible AM physicians regarding socio-demographic characteristics. In addition, the baseline characteristics of patients who were included resembled baseline characteristics of patients who were excluded from the study. These features suggest that our study to a high degree mirrors contemporary AMED use in outpatient settings.

Medication use was documented by the patients, which has the advantage of comprehensiveness, covering medications prescribed by different physicians as well as over-the-counter medication. Moreover, patient self-reporting of used medication avoids erroneous documentation of prescribed medication not taken by the patient. Since 2-year diary-keeping of all medication was not feasible, medication use was documented at each follow-up and patients may have forgotten some used AMED, leading to an underestimation of true use.[20] Recall bias may also have led to under-reporting of AEs suspected to be ADRs. Since salient events/items (e. g. adverse effects) are less likely to be under-reported than routine items (e. g, ongoing

medication)[20], under-reporting of AEs/ADRs is less likely than under-reporting of AMED use, making false-low frequency of ADRs to AMED due to recall bias unlikely. Over-reporting of medication use is unlikely[21-23] and any "over-reported" AEs suspected to be ADRs to AMED were subject to our safety analysis.

A limitation of our analysis of individual AEs is its restriction to patients with serious AEs or AEs where the physician or patient suspected an AMED could be the cause. Unidentified ADRs to AMED could be present among the other AEs. However, most of these were non-specific symptoms, pain conditions, respiratory or digestive diseases occurring frequently in the population, and no organ toxicity-related AEs were reported. Nevertheless, ADRs to AMED might develop insidiously, be erroneously ascribed to an underlying disease, remain undetected by patients assuming that AMED are natural and therefore *a priori* safe or occur too infrequently to be detected in the present cohort.[9;10] A 'natural equals safe' reporting bias is less likely with the participating physicians because these were repeatedly and explicitly encouraged to document any suspected adverse reactions from AMED or other causes.

Dropout rates increased from 3% after 3 months to 12% after 24 months. Some of these dropouts (and the 17 excluded patients without follow-up data) might represent withdrawals because of ADRs. However, considering the low frequency of confirmed ADRs in the evaluable patients, a more likely cause is the well known increasing propensity of subjects not to respond to repeated surveys, in particular when follow-up is prolonged over several years, as in the present study.

In the safety analysis, AEs were classified as 'confirmed ADR' (probable/possible relationship to AMED) or 'not confirmed ADRs' (improbable/no relationship/unable to evaluate). False-negative classifications (true ADR is not confirmed) are unlikely, since for all AMED for which an ADR was not confirmed, there was either no rational temporal relationship to the AE, or another cause (primary or concomitant illness,

another AMED or a non-AMED) was much more likely. However, false-positive classifications cannot be ruled out; some of the AEs classified as 'confirmed ADRs' with a 'possible' relation to AMED might instead be symptoms of primary or concomitant illness.

In this long-term cohort study, AEs suspected to be ADRs were documented independently by physicians and patients. When planning the study, this double documentation was chosen since not all patients were expected to visit their study physician regularly, and since patients may have ADRs to over-the-counter medication or from medication prescribed by other physicians. Patient documentation increased the number of confirmed ADRs from 14 to 21, demonstrating the value of using two documentation sources for medication safety.

We found confirmed ADRs in 3.0% of AMED users and at a frequency of one ADR per 382 patient-months of AMED use. This low frequency is in accordance with two other studies using prospective documentation of ADRs in all patients (0.3%[19] and 3.7% of patients[24], respectively). The somewhat lower frequency in the first study[19] may be due to its restriction to acute infections with a short follow-up (average 16 days).

Even lower estimates were given in two studies on AMED ampoules for injection (0.0002% of ampoules sold[25] – the corresponding ADR frequency in our present analysis is 0.027% of ampoules used – and 0.00001% of patient contacts[26]). Since these studies were based on spontaneous reporting[25] and physicians' retrospective recall of average 16 years' clinical experience[26] respectively, under-reporting is likely and the order of magnitude of ADR frequency in the two first studies (0.3%-3.7% of users) is probably a more realistic estimate.

We found a very low frequency of confirmed ADRs of severe intensity (0.3% of patients). Three types of ADRs to AMED were identified: local reactions to topical

application (patients no. 2-5, 7 and 10); systemic hypersensitivity (patient no. 11); and aggravation of pre-existing symptoms in sensitive patients – often difficult to distinguish from spontaneous symptom fluctuation (remaining 13 patients). No toxic or serious ADR occurred.

Conclusion

In this 2-year prospective study of 662 outpatients with chronic disease, we found a low frequency of ADRs and no serious ADRs to AMED. Study results suggest that long-term AMED therapy is generally well tolerated.

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